DETAILED ACTION

Applicant's response filed on 6/2/2011 is acknowledged and fully considered.

Status of Application, Amendments, And/Or Claims

The amendments of claims claim 9 and the addition of claim 24-36 have been made of record. Claims 1-8, 10, 11, and 19-23 are cancelled.

Claims 9, 12-18 and 24-36 are pending.

Claims 12-18 remain withdrawn for the reasons of record on page 2 of the office action of 2/3/2011 and claim 36 is withdrawn for being drawn to a non-elected invention of Group II (see Restriction Election of 8/3/2010).

Claims 9 and 24-35 are under examination.

Information Disclosure Statement

The IDSs filed on 1/31/2011 and 6/2/2011 have been considered.

Response to Arguments

Objections/Rejections – withdrawn

Specification

The objection to disclosure because the disclosure of nucleotide and/or amino acid sequences which are not in the sequence compliance as per 37 CFR 1.821-1.825 is withdrawn in view of Applicants' amendments to the specification filed on 6/2/2011.

Claim Rejections - 35 USC § 102

The rejection of claims 1-9 rejected under 35 U.S.C. 102(b) as being anticipated by WO 2000/52135 is withdrawn in view of Applicants cancellation of claim 1-8.

However, upon further consideration a new ground of rejection has been made under 35 USC 103(a).

The rejection of claims 1-9 rejected under 35 U.S.C. 102(b) as being anticipated by Fukuda et al (J. Biol. Chem. 262: 11952-11957, 1987) is withdrawn in view of Applicants cancellation of claim 1-8. However, upon further consideration a new ground of rejection has been made under 35 USC 103(a).

The rejection of claims 1-7, and 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin (US Patent No. 5,547,933) is withdrawn in view of Applicants cancellation of claim 1-8. However, upon further consideration a new ground of rejection has been made under 35 USC 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9, 24-30, and 33 rejected under 35 U.S.C. 103(a) as being unpatentable over Betenbaugh (WO 00/52135, see IDS).

The instant claims are broadly drawn to a process for the production of a highly active glycoprotein comprising:

expression of a highly active glycoprotein in an expression cell line, harboring at least one defect in the sugar nucleotide biosynthetic pathway of sialic acids and which is transfected with nucleic acid encoding the glycoprotein, in a medium supplemented with a concentration of at least one sialic acid precursor additive, the concentration being determined by a process comprising: (i) expression of a plurality of different sialylation forms of said glycoprotein by differential sialylation using different concentrations of at least one sialic acid precursor; and (ii) determination of the activity of the different sialylation forms in comparison with a reference glycoprotein in (a) suitable bioassay(s); and (iii) selection of the sialylation form with the higher/highest activity and determination of the concentration of the sialic acid precursor additive(s) which is correlated with the higher/highest activity level of said glycoprotein, wherein a partially sialylated glycoprotein is produced, wherein a sialic acid precursor additive is used which results in glycoproteins with natural sialic acid modifications

Betenbaugh teaches expressing a human transferrin protein in insect cell T. ni cell which has defect in adding sialic acid to a glycoprotein (page 73). Betenbaugh teaches that in insect cells, N-linked glycans attached to heterologous or homologous glycoproteins comprise either high mannose (Man9-5GlcNAc2) or truncated (Nan3-2GlcNAc2) oligosaccharides; occasionally comprising alpha(1,6)-fucose. Betenbaugh

teaches that T. ni cell (insect cell) show presence of limited level of partially elongated hybrid structures with one terminal Man branch and one branch with term Gal, GalNAc or another sugar and complex N-linked oligosaccharide (page 3, lines 16+). Betenbaugh teaches that production of sialylation of a recombinant protein (plasminogen) is observed in baculovirus-infected insect cells. Betenbaugh say that insect cells generate very little sialic acid compared to mammalian CHO cells (page 5, lines 17+). It is possible that similar lack or limitation may be observed in eukaryotes as well (page 5, lines 20+). Therefore, Betenbaugh suggests co-expressing sialyltransferase and other transferases and the proper acceptor substrates in order for production of sialylated and other complex glycoproteins in eukaryotes (page 5, lines23+). Betenbaugh teaches that manipulating carbohydrate processing pathways in inset and other eukaryotic cells so that the cells produce complex sialylated glycoproteins is useful for enhancing the value of eukaryotic expression system and increasing the application of heterologous cell expression products as vaccines, therapeutics, and diagnostic tools; and for lowering the biotechnology costs, since particular expression system can be selected based on efficiency of production rather than the capacity to produce particular glycoforms (page 6, lines15+). Betenbaugh teaches cell culture and quantitation of sialic acid (see page 87). Betenbaugh teaches doing in vitro activity from infected cells (page 87). Betenbaugh teaches that cell lines can be assessed for N-glycans attached to glycoproteins using techniques disclosed on page 57. Betenbaugh teaches to use a cell of interest which expresses the enzymeGlcNAc-2 epimerase (see claim 5 and 10). Betenbaugh teaches to use ManNAc supplementation to obtain substantial level of

New5Ac levels (page 78, lines23+). Although Betenbaugh does not teach performing assay using a sialylated protein and then optimize how much to sialylate a protein to achieve higher or maximum activity of the protein, it one of the routine in the art to achieve more activity of a protein by glycosylating the protein than a protein without glycosylation (e.g., Bonig et al). It is noted that Bonig et al is applied to support the skill of the art and not as a prior art.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a mammalian cell or insect which comprises a defect in the sialylation process and to co-express sialyltransferase and other transferases and the proper acceptor substrates in order for production of sialylated and other complex glycoproteins of interest such as human transferrin as taught by Betenbaugh. Additionally, one would have been motivated to do so because Betenbaugh teaches that manipulating carbohydrate processing pathways in inset and other eukaryotic cells so that the cells produce complex sialylated glycoproteins is useful for enhancing the value of eukaryotic expression system and increasing the application of heterologous cell expression products as vaccines, therapeutics, and diagnostic tools; and for lowering the biotechnology costs, since particular expression system can be selected based on efficiency of production rather than the capacity to produce particular glycoform (page 6, lines15+). Further, one would have a reasonable expectation of success in doing so because Betenbaugh teaches making a number of proteins such as human transferrin in insect cells as well human CHO cells.

Claims 31, 32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Betenbaugh (WO 00/52135, see IDS) in view of Muramatsu et al (J. Biochem. 94:799-810, 1983) and Foglin et al (Electronic J. of Biotech. 5: 243-250, 2002).

The instant claim is drawn to a process of producing a highly active glycoprotein comprising:

expression of a highly active glycoprotein in an expression cell line, harboring at least one defect in the sugar nucleotide biosynthetic pathway of sialic acids and which is transfected with nucleic acid encoding the glycoprotein, in a medium supplemented with a concentration of at least one sialic acid precursor additive, the concentration being determined by a process comprising: (i) expression of a plurality of different sialylation forms of said glycoprotein by differential sialylation using different concentrations of at least one sialic acid precursor; and (ii) determination of the activity of the different sialylation forms in comparison with a reference glycoprotein in (a) suitable bioassay(s); and (iii) selection of the sialylation form with the higher/highest activity and determination of the concentration of the sialic acid precursor additive(s) which is correlated with the higher/highest activity level of said glycoprotein, wherein the expression cell line is NM-F9 and wherein the glycoprotein is GM-CSF.

The teachings of Betenbaugh are summarized as set forth above. Betenbaugh does not teach using NM-F9 cells to express glycoprotein GM-CSF.

Muramatsu et al teach that F9 cell is used for making glycosylated protein (see abstract). It is noted that F9 cell is another name of NM-F9 (as suggested in US Pat.

No. 7,595,192, col. 14, lines 46+). Muramatsu et al do not teach making GM-CSF in F9 cells.

Foglin et al disclose that glycoprotein GM-CSF produced in various cells including COS and CHO cells (page 244, GM-CSF preparation).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use F9 cells (aka NM-F9) as taught by Muramatsu to express GM-CSF which is a glycoprotein as taught by Foglin et al by using a process which can increase glycosylation as taught by Betebaugh. Additionally, one would have been motivated to do so because Foglin et al teach that GM-CSF is a glycoprotein and because Muramatsu et al teach that F9 cells make glycosylated proteins. Additionally, one of the ordinary skill in the art would be motivated to use F9 cells because the teratocarcinoma F9 cell is one of the highly used cell line for protein expression and cell differentiation studies. Further, one would have a reasonable expectation of success in using F9 cells to make GM-CSF using Betebaugh because GM-CSF is a glycoprotein as taught by Fogolin et al and it is routine to make a glycosylated protein in F9 cells as taught by Muramatsu et al.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(f) he did not himself invent the subject matter sought to be patented.

Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Fogolin et al (Electronic J. of Biotech. 5: 243-250, 2002).

The instant claim is drawn to glycoprotein GM-CSF which is producible by the process of claim 34.

Fogolin et al disclose that glycoprotein GM-CSF produced in various cells including COS and CHO cells (page 244, GM-CSF preparation). Therefore, the prior art of record anticipates the instantly claimed invention.

[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Claim 35 is rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The instantly claimed product which is glycoprotein GM-CSF (or glycosylated GM-CSF) is the same or similar product which is available by Sigma-Aldrich and has been available prior to 2004 (see search Result-Google and see the Sigma-Aldrich catalog).

[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GYAN CHANDRA whose telephone number is (571)272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gyan Chandra/
Primary Examiner, Art Unit 1646